REMARKS

Reconsideration is respectfully requested in view of the foregoing amendments, the following remarks and the attached articles.

By this Amendment claims 7, 10 and 11 have been amended. The amendments to these claims are fully supported in the as-filed specification.

Rejection under 35USC § 112, first paragraph

According to the Examiner, claims 7-12 stand rejected due to the specification being not enabling for the absolute prevention of RAU or RAS.

In order to overcome this rejection, Applicant has amended independent claim 7 to delete "preventing", and by inserting "for preventing the occurrence of new, recurrent oral aphthous ulcers". This amendment is supported in the as-filed specification at page 7, lines 13-14.

The clinical trial disclosed in the present specification was also the subject of a scientific publication, which is enclosed herewith as Annex 1 ("The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration" Nolan et al. *J. Oral Path. Med* (2006) (461-5)).

As stated in Annex 1, the following results were achieved (see Results, page 462, right-hand column to page 463, left-hand column):

(1) a statistically significant ($p=0.04$) reduction of ulcers on day 5 in patients treated with HA(1.65 ±0.25), when compared to the placebo group (2.4±0.26) (see Table 2);

(2) a statistically significant ($p=0.047$) reduction on day 4 of new ulcer **occurrence** in patients treated with HA(2), when compared to the placebo group (10) (see Table 4); and,

(3) a statistically significant ($P<0.001$) increase of patients free from ulcers on day 7 in patients treated with HA (24), when compared with patients treated with placebo (19) see Table 3.

The results reported at item (2) provide clear evidence that hyaluronic acid is also able to prevent or reduce new ulcer occurrence in patients affected by ROAU.

Accordingly, the rejection under § 112, first paragraph, has been overcome and should be withdrawn.

Rejection under 35USC § 103(a)

Claims 7-12 stand rejected under § 103(a) as being obvious over EP444492 (DI SCHIENA) in view of the Saxen et al. article on the following grounds:

(i) Di Schiena teaches a pharmaceutical composition comprising from 0.2 to 10% sodium hylauronate having a molecular weight between 800,000 and 4,000,00 for the treatment of oral stomatitis.

Di Schiena does not exemplify the treatment of recurrent aphthous stomatitis using the composition. Saxen et al teach that recurrent aphthous ulcers are a common disorders and the most common treatment is topical anesthetics and topical steroids for pain management. Saxen et al. teach a study in which adults having aphthous ulcers were treated with 3% diclofenac in 2.5% hyaluronan, 2.5% hyaluronan or 3% viscous lidocaine. A reduction of pain was observed 10 minutes after application with no significant difference between the three topical agents [see the Abstract].

(ii) It would have been obvious to one of ordinary skill in the art at the time the invention was made to treat ROAU with the composition of Di Schiena, who teaches the composition for the treatment of stomatitis in general and the skilled artisan would expect that such a composition to be useful for the treatment of ROAU. Furthermore, Saxen et al. teaches that hyaluronan is effective in the treatment of recurrent aphthous ulcers.

(i) Applicant submits herewith as Annex 2 a photocopy from the Merck manual 18th edition, pages 755-757 wherein it is reported **that stomatitis is a widespread inflammation of the mouth** which may be caused by (bacterial, viral or fungal) **infections, systemic diseases**, a **physical agent or other causes** such as hypovitaminosis, iron deficiency or agranulocytosis, cheek biting, mouth breathing, ill fitting dentures, nursing bottles, excessive use of alcohol, tobacco, hot foods, etc.

In the Merck Manual, Recurrent Aphthous Stomatitis, or Recurrent Aphthous ulcers, is considered as **a disease apart from the above discussed stomatitis**,

In fact, Applicant encloses as Annex 3 a photocopy from "Oral Pathology", Third Edition, J.V. Soames and J.C. Southam, Chapter 12, pages 211-227, wherein the classification of oral ulcerations is given at page 211, Table 12.1, which affirms that RAS belongs to the class of idiopathic diseases, in other words, a disease having **an unknown etiology**.

It follows therefore that one of ordinary skill in the art from a reading of Di Schiena, which discloses that high molecular weight hyaluronic acid was effective in the treatment of stomatitis, was unable to infer that the same type of active ingredient would also be effective in the treatment of RAS, which is a **pathology separate and apart** from stomatitis.

It is submitted that one of ordinary skill in the art would be unable to overcome the deficiency in the Di Schiena teaching even with the benefit of the Saxen teaching.

First, the molecular weight of the Hyaluronan used by Saxen et al. is **not** specified.

Secondly, the topical compositions HA + DICLO, and HA **alone** utilized by Saxen were able to reduce pain after only 10 minutes, whereas for an extended period of time (2 hrs. to 6hrs.), **only the association of diclofenac and hyaluronan provided an effective result** in reducing pain (see the Abstract). Moreover, as is also acknowledged by the same authors at page 358, right-hand column, lines 8-10 of the chapter

"RESULTS, **no significant change in ulcer diameter** was observed throughout the trial." (See also Table 2, page 359.)

It follows from the foregoing that the only inferences that the skilled person would have drawn from Saxen et al. were:

- when hyaluronan was administered **as the sole active ingredient,** it was able to provide pain relief **only 10 minutes after its administration**;
- that the same active ingredient, when associated with Diclofenac, was able to reduce pain for an extended period of time (2 to 6 hrs. from administration); and,
- either when administered alone or in association with Diclofenac, HA **was unable to modify the size of the lesions and, consequently, to reduce the number of ulcers.**

It follows from the foregoing that a person of ordinary skill in the art from a reading of Saxen et al.'s disclosure would have been motivated to think that hyaluronan, and specifically the high molecular weight hyaluronic acid disclosed by Di Schiena, was **not** effective in the treatment of RAS.

Consequently, the Saxen et al. teaching when added or combined with Di Schiena **would, indeed, have taught away** from the concept of the claimed method for the treatment of RAS, which consists of the administration of high molecular weight hyaluronic acid or a salt thereof as the sole active ingredient.

As a matter of fact, from the combined teachings of Saxen and Di Schiena **it is quite surprising** to have found that high molecular weight hyaluronic acid, when administered as the sole active ingredient to patients affected by RAS, was able to not only reduce pain, but also:

- to **reduce** the number of ulcers **already formed** as can be seen by the results from Table 2 of Annex 1 and also from item (1) above regarding the statistically significant reduction of ulcers;

- to **prevent or reduce** new ulcer occurrences as shown in item (2) above and Table 4 of Annex 1;

- to increase the number of patients free from ulcers at the end of the treatment which is statistically significant (see Table 4 and also item 3 above).

(ii) Applicant has already stressed that stomatitis as defined in the Merck Manual, namely, a widespread inflammation of the mouth which can be caused by bacterial, viral, or fungal infections, systemic diseases and the other causes listed above, is a disease which is separate and apart from RAS, and which **cannot be said to be associated** with Recurrent Aphthous Stomatitis in any manner.

Moreover, the skilled artisan would, at most, have inferred from Di Schiena that high molecular weight HA is able to restore the inflamed oral tissue, but he/she would **not possibly have** inferred that HA, when administered in patients affected by RAS, not only reduces the number of recurrent oral aphthous ulcers **already formed** (see (1) above), but is also able **to reduce the frequency of new ulcers** (see (2) above), **which it should not be forgotten, has an unknown cause.**

It follows therefore that the Examiner's conclusion that "*being known from Di Schiena that high molecular weight hyaluronic acid is used in the treatment of stomatitis in general, the skilled artisan would expect that such a composition is also useful in the treatment of RAS*", **seems to be rather simplistic**.

Moreover, Saxen et al.'s teaching that administering only HA to patients affected by RAS is **unable** to reduce the diameter of the lesion, and therefore reduce the number of ulcers, **goes in a completely opposite direction from the conclusions posited by the Examiner**.

Therefore, one of ordinary skill in the art would be unable to arrive at the presently claimed method from the combination of Saxen et al. and Di Schiena.

In view of the foregoing and Applicant's amendments to claim 7, which included inserting "consisting" as the transitional phrase, as well as the evidence submitted, serve to distinguish over the art applied by the Examiner.

Accordingly, the § 103(a) rejection has been overcome and should be withdrawn.

Since the rejections of record have been overcome, the issuance of a Notice of Allowance is respectfully solicited.

Please charge any fees which may be due and which have not been submitted herewith to our Deposit Account No. 01-0035.

Respectfully submitted,

ABELMAN, FRAYNE & SCHWAB
Attorneys for Applicant

By 
Jay S. Cinamon
Attorney for Applicant
Reg. No. 24,156

666 Third Avenue
New York, NY 10017-5621
Tel.: (212) 949-9022
Fax: (212) 949-9190

J Oral Pathol Med (2006) 35: 461–5

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ANNEX 61

The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration

A. Nolan, C. Baillie, J. Badminton, M. Rudralingham, R. A. Seymour

School of Dental Sciences, University of Newcastle upon Tyne, Framlington Place, Newcastle upon Tyne, UK

BACKGROUND: The aim of this study was to evaluate the efficacy of a topical hyaluronic acid (HA) preparation (0.2%) in the management of recurrent aphthous ulceration (RAU).

METHODS: One hundred and twenty patients with RAU participated in a randomized, placebo controlled, double-blind trial to evaluate the efficacy of the topical HA and preparation. Outcome measures include soreness relief on immediate application (recorded over 60 min). Thereafter, patients completed a log diary recording soreness from the ulcers, occurrence of new ulcers and ulcer-duration.

RESULTS: Both topical HA and placebo resulted in a significant reduction in ulcer soreness following immediate application ($P = 0.0004$). Throughout the rest of the investigation period, there was no significant differences ($P > 0.05$) between the treatments for reducing soreness. Patients treated with topical HA recorded few ulcers on day 5 of the investigation than those treated with placebo ($P < 0.001$). Likewise, the occurrence of new ulcers was lower in the HA treated group on day 4 when compared with placebo ($P = 0.047$).

CONCLUSION: Topical HA (0.2%) may be of benefit in the management of RAU. Immediate reduction of symptoms appears to be a barrier effect.

J Oral Pathol Med (2006) 35: 461–5

Keywords: efficacy; recurrent aphthous ulceration; topical hyaluronic acid

Introduction

Recurrent aphthous ulceration (RAU) is a common inflammatory condition of unknown aetiology, although a variety of predisposing and other risk factors have been identified. It is the most common form of oral ulceration and approximately 20% of the population will suffer from RAU at some time in their lives (1)

Correspondence: Dr Anita Nolan, Oral Medicine, Dundee Dental Hospital & School, Park Place, Dundee, DD1 4 HR, UK. Tel.: 01382 635969, Fax: 01382 425783, E-mail: anita.nolan@dundee.ac.uk
Accepted for publication February 7, 2006

Topical preparations appear to be the main agents used in the treatments of RAU, especially those with an anti-inflammatory action. However, for such agents to be effective, they should be easy to apply and retained at the site of ulceration for as long as possible. The active ingredient needs to be released from the delivery vehicle and exhibit substantivity.

Hyaluronic acid (HA) is a linear polymer of glucuronic acid N-acetylglucosamine disaccharide. Most cells have the capacity to synthesis HA during some point of their cell cycle. The main function of HA appears to be in tissue healing. In this process, HA is implicated in a range of activities including activation and moderation of the inflammatory responses, promoting cell proliferation, migration and angiogenesis, promoting re-epithelization via proliferation of basal keratinocytes and reducing collagen disposition and scarring (2). Animal studies have shown that HA can promote healing in a variety of tissues (2). Clinical studies have shown that topical application of HA promotes healing of both venous leg ulcers (3), and the nasal mucosa after surgery (4). It also has been shown to reduce the incidence of high-grade radio-epithelitis in patients who have undergone radiotherapy for head and neck, breast or pelvic carcinomas (5). A hyaluronic preparation is available commercially, but its usefulness for the management of RAU has not been proved. The aim of the present study was to carry out randomized, placebo controlled investigation into the efficiency of a topical HA gel 0.2% (RF02 APH) in the relief of symptoms of RAU.

Materials and method

One hundred and twenty adult patients who presented with RAU participated in the study. All patients underwent a full haematological screening before entering the study. The parameters measured included FBC, serum B12, red cell folate, serum ferritin and endomysial antibody. Only patients whose values were within the normal range were included in the study. Other entry criteria included a clear history of RAU occurring at least twice a year and to have at least one ulcer present prior to dosing. Patients were excluded if they

exhibited any underlying haematological disorder, taking non-steroidal anti-inflammatory drugs (NSAIDs), immunosuppressants, other anti-inflammatory agents or chemotherapeutic drugs, suffering from an uncorrected dietary defect, or had a history of probable sensitivity to mouthwash or toothpaste.

The protocol for the study had received approval from the local joint Ethics Committee. Patients for the study were enrolled from the Oral Medicine Clinic, Newcastle Dental Hospital. Eligible patients had to present with discomfort arising from an ulcer. For these patients a topical application of HA gel 0.2% or identical placebo was applied by a Clinician to the ulcerated area. Allocation of the gel to the patient population was randomized and double-blind. Patients were instructed how to apply gel for subsequent applications.

Following first dosing, patients were retained in the clinic and asked to record on 100 mm visual analogue scales (VAS) the discomfort arising from the ulcerated area. The boundaries of the scale were marked 'no soreness' and 'worst possible soreness'. Recordings were made at baseline (before gel application) and at 5, 10, 15, 20, 30, 45, 60, 120, 180 and 240 min after dosing. The first 60 min of the recording were supervised and the remaining observations were carried out on a log diary provided to the patients on discharge. On completion of the first 60 min, patients were given a sufficient supply of gel to apply two to three times per day for the next 7 days. Patients were instructed to apply the gel after breakfast and after their evening meal and at one other time if desired. Times of gel application were recorded in the log diaries. Further discomfort recordings were made 1 h after application for 7 days. In addition to recording discomfort, patients were also asked to record number of ulcers present in their mouth and the occurrence of any new ulcers during the treatment period. Completed log diaries were reviewed at a clinical appointment on day 8 and any remaining gel returned. At this appointment, patients were asked to make an overall assessment of the gel on 5-point description scale (very poor, poor, moderate, good and very good). Patients were also asked whether they would use the gel again in the management of their RAU.

Statistical analysis

The main outcome measure of this study was the relief of soreness based upon repeated VAS recording. These scales have been used extensively in the measurement of pain and other subjective responses, but have not been utilized in the assessment of therapies for the treatment of RAU. The power calculation for this study was therefore based upon observed standard deviations from analgesic efficiency studies. Assuming a standard deviation of 15 mm on the 100 mm VAS, a power calculation based upon a sample size of 60 patients per group and alpha level of 0.05 would allow the detection of a mean difference between treatments of 10 mm on the VAS with 84% power.

Analysis of variance according to the model of repeated measurements within-between subjects, integrated by covariate analysis at the basal time was used to assess differences between treatment groups for soreness scores and ulcer history (number of ulcers present in the mouth each day and number of new ulcers). A Pearson chi-square test was used to assess differences between treatment groups for the distribution of patients' scores for their overall assessment of the medication. P-value < 0.05 was considered statistically significant.

Results

A total of 120 patients were enrolled into the study and completed the first supervised part of the investigation and returned their log diaries. Four log diaries were subsequently rejected because of protocol violations. Of the remaining 116 patients, 60 received HA 0.2% and the remainder placebo gel. Demographic details of patients together with details of their baseline ulcer history and soreness scores are shown in Table 1. The number of ulcers and baseline soreness scores were similar for the two treatment groups ($P > 0.05$).

Following initial application, patients in both treatment groups reported a rapid reduction ($P = 0.0004$) in their discomfort scores arising for their ulcers (Fig. 1). This level of reduction was sustained for both treatment groups for about 30 min. There after scores started to return to baseline. A similar position was observed for the subsequent 3 h, and throughout the rest of the 7 day observation period (data not shown). The number of

Table 1 Demographic details of patients and baseline ulcer study for those who participated in study

	Placebo	*HA 0.2%*
Total number	60	60
Male	17	18
Female	43	42
Average age	36.65	37.05
Ethnic origin	58 White 2 Asian	58 White 2 Asian
	3	1
Protocol violators		
Mean baseline soreness scores (mm) as recorded on 100 mm VAS	52.28	42.03
Average number of ulcers at baseline	2.51	1.95

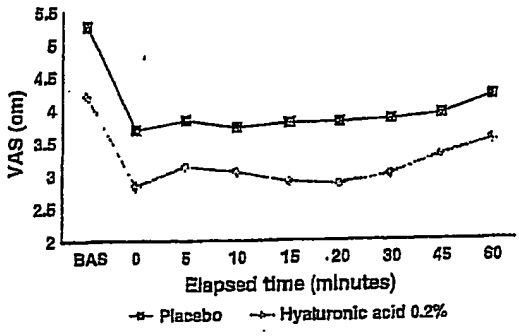

Figure 1 VAS Scores Post-Gel Application.

Table 2 Mean number of ulcers (±SEM) for each treatment group during the 7 day investigation period

Time (days)	*Placebo*	*HA 0.2%*	*Significance between groups*
Baseline	2.5 ± 0.24	1.96 ± 0.24	0.12
Day 2	2.7 ± 0.25	2.2 ± 0.25	0.16
Day 3	2.58 ± 0.25	2.13 ± 0.25	0.21
Day 4	2.48 ± 0.25	1.88 ± 0.25	0.09
Day 5	2.4 ± 0.26	1.65 ± 0.25	0.04
Day 6	2.2 ± 0.28	1.56 ± 0.28	0.11
Day 7	2.0 ± 0.28	1.53 ± 0.28	0.22

Table 3 Ulcer history during 7-day investigation period for patients treated with hyaluronic acid and placebo

Ulcer count at baseline	*Number of patients*	*Number of patients free from ulcers*
(a) Hyaluronic acid		
1	37	19
2	10	3
3	5	1
4	2	0
5	2	0
6	2	0
8	2	1
Total	60	24
(b) Placebo		
1	28	13
2	11	3
3	7	1
4	5	1
5	1	1
6	5	0
7	2	0
10	1	0
Total	60	19

ulcers before medication was similar for both treatment groups (Table 2). Patients were asked to record each day the number of ulcers present in their mouth and mean number of ulcers for each treatment is shown in Table 2. There was a slight decline in the number of ulcers, irrespective of treatments, over the 7 day observation period. However on day 5 patients in the RF02APH (study compound) group had significantly fewer ulcers than those treated with placebo. More details of ulcer history with respect to number of ulcers per patient at baseline compound to number of patients free from ulcers after 7-days of treatment is shown in Table 3a and b. Although there is a significant decline in both treatment groups ($P < 0.001$), there was no difference in ulcer history between treatments.

In both treatment groups, new ulcers occurred throughout the investigation period. On day 4 the incidence of new ulcer occurrence was significantly lower in the RF02APH (active) group when compared with placebo treatment patients ($P = 0.047$). For the other days, the new ulcer occurrence rate was similar (Table 4).

Patients overall assessment of their treatments is shown in Table 5. There was no significant difference

Table 4 Number of patients with ulcer occurrence during 7-day investigation period

Day	*Placebo*	*HA 0.2%*
1	16	12
2	5	5
3	5	1
4	10*	2
5	7	7
6	5	2
Total	48	29

*Significant difference between treatment groups $P = 0.047$.

Table 5 Distribution of scores from patients overall assessment of their treatment

Score	*Placebo*	*HA 0.2%*
Very good	10	17
Good	11	15
Moderate	17	12
Poor	12	10
Very poor	7	5
Not recorded	3	1

($P = 0.075$) between treatments in the distribution of scores. Unwanted effects were few and showed no difference between treatment groups.

Discussion

Topical medications appear to be the first choice treatment for RAU. Such preparations do have limitations with respect to drug delivery, subsequent compliance and retention on the oral mucosa. These features probably impact significantly on the efficacy of the agent, but do present challenges to the pharmaceutical industry for appropriate development.

Parameters used to evaluate the outcome of treatments in the management of oral ulceration include 'ulcer days index' (number of days free from ulcers), incidence of ulceration, duration of ulceration, severity of pain and user preference (6). The 'ulcer day index' is the sum of the number of ulcers each day over a period, usually 4–8 weeks. It indicates the severity of the episode and reflects the mean prevalence and duration of ulcers as well as the number of ulcer-free days in a specific period. The incidence of ulceration is the number of new ulcers forming within a specified period, usually a period of no less <4 weeks. The duration of ulceration is the mean duration of individual ulcers. Pain can be assessed subjectively by patients on pain scores. User preference allows the patient to subjectively indicate the acceptability of a particular product.

The most significant outcome of this study was the immediate and sustained reduction in pain scores after application of HA 0.2% and placebo. Both preparations (RF02APH and placebo) were based on the same formulation with the only exception of HA, substituted, in the latter by inert material) caused a significant immediate reduction in discomfort following applica-

tion. This would suggest some protective or barrier function arising from placement of this specific gel. The effects seemed to last for at least 30 min and there was no difference in efficacy between treatment groups. This protective or barrier for property arising from the gel may support further the use of topical medications in the management of symptoms arising from RAU.

We also observed a reduction in the number of ulcers over time in the HA treated group. This was observed on day 5 and would imply that exogenous high molecular weight HA is promoting healing when compared with placebo treatment. Indeed this is a major physiological property of HA. HA was only applied topically in this study, thus the physical chemical properties are important in relation to efficacy. HA is a hygroscopic macromolecule and solutions are highly osmotic. In the skin and perhaps on the oral mucosa, this property is likely to be relevant in controlling tissue hydration during periods of change such as the inflammatory process or response to tissue injury. This is also particular relevance for cell proliferation and migration, when HA synthesis contributes to local foci of tissue hydration. This results in the weakening of cell anchorage to the extra cellular matrix, allowing temporary detachment to facilitate cell migration and division (7). In the hydrated state, much of the water around the HA molecule is immobilized which results in restriction of movement of water and small molecules (8). The highly viscous native of HA also contributes to retardation of viral-and bacterial passage through the HA-rich pericellular zone (9, 10). In inflammation, HA may also have a moderating effect through free-radical scavenging (11, 12), antioxidant effect (13), as well as through exclusion of tissue degrading enzymes from the immediate cellular environment and from other structural components of the extra cellular matrix (14). All of these properties are likely to contribute to the healing process and may account for the reduction in the ulcers found in the treatment group at day 5. Some of these properties may also account for the reduction is the occurrence rate also observed in the active treatment group on day 4.

This double blind randomized controlled trial looks particularly at the efficacy of HA 0.2% in the management pain associated with RAU as well as measuring the patients' overall acceptability of the product. We also made observations on the possible effect of HA 0.2% on ulcer duration, although the time period over which the ulcers were recorded was too short to make accurate duration measurements. Other studies on the effect of topical preparations on the management of RAU use a variety of different parameters outlined above. This, therefore, makes direct comparison between HA and other topical preparation difficult. Nevertheless, pain scores are commonly used, so some comparisons can be made.

The effect of chlorhexidine gluconate mouth rinses on RAU have been studied and a recent review of these studies (15) concluded that chlorhexidine mouthwash did not influence the incidence of mouth ulcers, but that it reduces the severity of each episode of ulceration. Evidence for this conclusion has come from three randomized clinical trials of crossover design (16–18). Overall, chlorhexidine appears to play a role in the management of aphthous ulceration, possibly by reducing the prevalence of secondary infection, but it does not provide significant immediate pain relief.

Topical steroids are commonly used in the management of RAU. Only one crossover, randomized controlled trial demonstrated a significant reduction in pain compared with placebo, but showed no effect on reducing the frequency of RAU occurrence (19). The remaining studies give some weak evidence of a reduction in pain and ulcer duration, without significant adverse effects (20–25). It was also reported that most users preferred topical steroids to control preparations (21–24). The evidence, therefore suggests that topical steroids are of value to this group of patients. Nevertheless, HA 0.2% offers advantages over steroids in that it is safe in all patients including infants and pregnant women, in whom there may be reluctance to use steroids.

Amlexanox 5% is a further topical agent used in the management of RAU. This agent possesses both anti-inflammatory and anti-allergic properties. Results from various clinical trials have demonstrated that amlexanox facilitates the healing of oral ulcers by reducing their duration by up to 2 days (26), accelerates the resolution of ulcer pain and healing (27, 28). A recent study has also shown that early application of amlexanox in the prodromal stage of RAU does appear to abort an outbreak (29).

This product, therefore, is of value in the overall management of RAU, particularly if applied at very early stages. HA 0.2% can be applied at any stage of ulceration and provides immediate reduction in pain levels, thereby offering a different therapeutic approach to patients.

It would appear therefore, that chlorhexidine can reduce the duration of ulcers, but can cause some discomfort to such patients on initial application. Amlexanox (5%) hastens the healing process of ulcers and the duration to complete pain relief. Topical steroids help reduce the duration of ulcers, but provide little pain relief. Additionally, although the risk of steroid complications is low if used for a limited period of time and used correctly, topical steroids cannot be used in all patients. HA 0.5% provides immediate pain relief on application regardless of the stage of ulceration. It can be used in all individual including infants and pregnant women without risk of complications or drug interactions. There is no risk of overdose and can be safely recommended to individuals who may not follow instructions easily. It s widely available as an over the counter preparation and does not cause any discomfort, making it acceptable to children. In addition, it would appear to accelerate healing, although further studies are recommended to evaluate this property.

Topical applications of HA 0.2% does appear to be of benefit in the management of RAU. Immediate application reduces discomfort but this is purely a barrier or protective mechanism from stimuli arising in the oral environment. HA 0.2% may be of benefit in promoting

ANNEX 2

THE MERCK MANUAL

CENTENNIAL EDITION

1st Edition – 1899
2nd Edition – 1901
3rd Edition – 1905
4th Edition – 1911
5th Edition – 1923
6th Edition – 1934
7th Edition – 1940
8th Edition – 1950
9th Edition – 1956
10th Edition – 1961
11th Edition – 1966
12th Edition – 1972
13th Edition – 1977
14th Edition – 1982
15th Edition – 1987
16th Edition – 1992
17th Edition – 1999

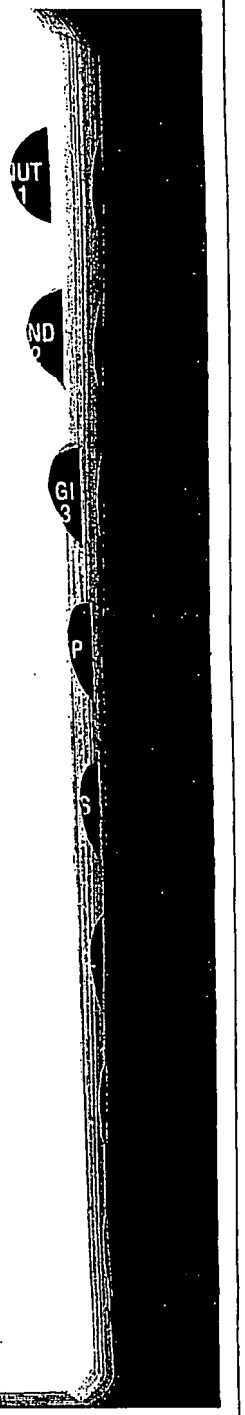

TABLE 105–1. SOME DISORDERS OF THE ORAL REGION BY PREDOMINANT SITE OF INVOLVEMENT (*Continued*)

Site	Disorder	Description
Tongue and floor of mouth *(continued)*	Dermoid cyst	Swollen floor of mouth
	Enlargement of tongue	Localized or generalized depending on how many teeth are missing; adjacent teeth may indent tongue
	Fissured (scrotal) tongue	Deep furrows in lateral and dorsal areas
	Glossitis	Red, painful tongue; often secondary to another condition; allergic, or idiopathic
	Hairy tongue	Dark, elongated filiform papillae
	Linea alba	Thin white line on edges of tongue, usually bilateral
	Lingual thyroid nodule	Smooth-surfaced nodular mass of thyroid tissue follicles, on the far posterior dorsum of tongue, usually at the midline
	Ludwig's angina	Can compromise the airway by forcing the tongue superiorly and posteriorly
	Median rhomboid glossitis	Red (usually) patch in midline of tongue, without papillae
	Neurilemoma	Persistent swelling, sometimes at site of prior trauma
	Pernicious anemia	Smooth, pale tongue, often with glossodynia or glossopyrosis
	Ranula	Large mucocele penetrating the mylohyoid muscle, may plunge deep into the neck; swollen floor of mouth
	Thyroglossal duct cyst	Midline swelling that moves upward when tongue protrudes
	Tuberculosis	Ulcers on dorsum, cervical adenopathy
Salivary glands	Benign lymphoepithelial lesion (Mikulicz's disease)	Unilateral or bilateral enlargement of salivary glands; often with dry mouth and eyes
	Sialadenitis	Swelling, often painful, benign
	Sialolithiasis	Swelling (eg, of floor of mouth) that increases at mealtime or after eating a pickle
	Sjögren's syndrome	See Ch. 50
	Xerostomia	Dry mouth

veolar bone covering part of the roots of teeth. Nonkeratinized mucosa occurs over alveolar bone furthest from the crowns of teeth, inside the lips, in the cheeks, on the sides and undersurface of the tongue, on the soft palate, and on the floor of the mouth. Keratinized tissue that occurs in normally nonkeratinized areas appears white. This abnormal condition, called leukoplakia, requires a biopsy because it may be precancerous.

The **palate** is involved in normal vocal resonance and articulation. The anterior hard palate is the site of the incisive papilla behind the central incisors. Behind it are the rugae, firm ridges that keep food from slipping as the tongue moves beneath it. The bones of the soft palate should rise symmetrically when the patient says "ah."

The **uvula** hangs in the midline at the free end of the soft palate. It varies greatly in length. A long uvula or excess velopharyngeal tissue is associated with snoring and in some persons may predispose to obstructive sleep apnea (see SLEEP APNEA SYNDROMES in Ch. 173).

The dorsal surface of the tongue is covered by numerous whitish elevations, the filiform papillae. Interspersed among them are isolated reddish prominences, the fungiform papillae, occurring mostly on the anterior part of the tongue. The circumvallate papillae, which are considerably larger, lie posteriorly. They do not project from the tongue but are surrounded by a trench. The foliate papillae appear as a series of parallel slitlike folds on the lateral borders of the tongue, near the anterior pillars of the fauces. They vary in length and can easily be confused with lesions. Lingual tonsils may be considered components of Waldeyer's ring and are seen posteriorly at the back of the tongue.

The lingual nerves (branches of the 5th cranial nerves) supply general sensory innervation, and the chorda tympani fibers (of the 7th cranial nerves) innervate the taste buds of the anterior 2/3 of the tongue. Behind the circumvallate papillae, the glossopharyngeal nerves (9th cranial nerves) provide the sensations of touch and taste. Nerve integrity can be determined by testing taste on both sides of the dorsum of the tongue with sugar, salt, vinegar, and quinine. Sweet and salty taste receptors are located at and near the tip; sour, on the sides; and bitter, on the most posterior part of the tongue. The hypoglossal nerves (12th cranial nerves) control movement of the tongue.

On each side, the **floor of the mouth** is marked anteriorly near the midline by the opening of Wharton's duct, which drains the ipsilateral submandibular and sublingual glands.

The major **salivary glands** are the paired parotid, submandibular, and sublingual glands. Most oral mucosal surfaces contain many minor mucus-secreting salivary glands. Abnormal sublingual and submandibular glands can be felt when the floor of the mouth is palpated bimanually. A parotid enlargement occurs preauricularly, or overlying the mandibular ramus.

Many disorders can affect the oral region (see TABLE 105–1 and elsewhere in THE MANUAL). Benign lesions of the oral region are common; bilateral, bilateral oral cancers are rare. Cleft lip and cleft palate are discussed in Ch. 261.

INFLAMMATION OF THE ORAL MUCOSA

Inflammation of the mouth may be caused by infection, systemic disease, or a physical agent. When widespread, it constitutes **stomatitis.**

Bacterial infections: Usually, the causative agent is streptococci. *Mycobacterium tuberculosis* can produce oral ulcers inoculated by sputum from the lungs. Syphilis can produce a primary chancre. If untreated, syphilis may produce secondary mucous patches and a tertiary gumma (see Ch. 164). *Neisseria gonorrhea* produces burning ulcerations of the gingiva and tongue as well as pharyngitis. Cervicofacial actinomycosis (lumpy jaw) may resemble a fungal infection but is bacterial (see ACTINOMYCOSIS in Ch. 157). Yellow ("sulfur") granules in purulent exudate are pathognomonic.

Noma (gangrenous stomatitis) is a nonspecific, mainly fusospirochetal bacterial infection in which severe, even full-thickness, tissue destruction occurs in a debilitated person. It can be considered an extreme form of acute necrotizing ulcerative gingivitis (see Ch. 106), which normally affects only the gingivae.

Viral infections: The mouth is a common site of viral infections. Some are clinically significant, primarily in immunocompromised persons. Herpesvirus infections are discussed below.

Fungal infections: *Candida albicans* and related species are normal oral flora. They can overgrow in persons who have taken antibiotics (particularly broad-spectrum) or corticosteroids and in debilitated persons, such as AIDS patients. Candidiasis generally looks like cheese curds, which when wiped off, leave a raw, bleeding surface. The chronic erythematous and erosive forms are more difficult to recognize (see also CANDIDIASIS in Ch. 113). Oral and paraoral lesions occur infrequently in blastomycosis, histoplasmosis, coccidioidomycosis, cryptococcosis (mainly in debilitated patients), and mucormycosis (particularly in the sinuses of diabetics—see Ch. 158).

Systemic diseases: Scarlet fever produces a strawberry tongue due to hypertrophied fungiform papillae. Pellagra produces a smooth, fiery red tongue, painful mouth, and mucosal ulcerations. Hemorrhagic oral

lesions may occur in erythema multiforme (see below), scurvy, leukemia, thrombocytopenic purpura, and platelet disorders. Unprovoked bleeding, decreased salivation, and an ammonia-like odor accompany uremic stomatitis. The mucocutaneous lymph node syndrome (Kawasaki syndrome) affects children, causing erythema of the lips and oral mucosa (see KAWASAKI SYNDROME in Ch. 265).

Other causes: Stomatitis may result from hypovitaminosis (particularly lack of the B vitamins or vitamin C), iron-deficiency anemia with dysphagia (as in Plummer-Vinson syndrome), or agranulocytosis. Cheek biting, mouth breathing, jagged teeth, orthodontic appliances, ill-fitting dentures, or nursing bottles with nipples that are hard or too long may cause local mucosal injury. Xerostomia (see ORAL FINDINGS IN SYSTEMIC DISORDERS in Ch. 103) predisposes the mouth to infection. Stomatitis may follow excessive use of alcohol, tobacco, hot foods, or spices as well as sensitization to ingredients in toothpaste, mouthwash, candy dyes, lipstick, or, rarely, acrylic dentures. Occupational exposure to dyes, heavy metals, acid fumes, or metal or mineral dust and the use of drugs, such as iodides and barbiturates (which may cause the Stevens-Johnson syndrome), may produce oral lesions. Rarely, contact stomatitis may result from sensitivity to dental materials. Acrodynia may be caused by a toxic reaction to mercury or by hypersensitivity to various substances; exposure to mercury is now rare. Acrodynia occurs in children and is characterized by oral ulcerations, profuse salivation, bruxism (clenching or grinding of teeth), and loss of teeth.

Pseudomembranous (membranous) stomatitis, an inflammatory reaction that produces a membranelike exudate, may be caused by chemical irritants (eg, gold, iodides) or by bacteria (eg, streptococci, staphylococci, gonococci, *Corynebacterium diphtheriae*). Fever, lymphadenopathy, and malaise may occur.

HERPESVIRUS INFECTIONS

Primary herpes simplex (typically contracted as a child) results in **acute herpetic gingivostomatitis.** It is usually due to herpes simplex virus type 1 but, through oral-genital contact, can be due to herpes simplex virus type 2. It begins as small vesicles that quickly rupture to form ulcers. When initially localized, it may resemble aphthous stomatitis, but primary herpes always affects the attached gingiva and may affect other tissues, whereas aphthous stomatitis never affects attached gingiva. With herpes, fever and pain are often present. Difficulty in eating and drinking may lead to dehydration. The infection typically lasts 10 to 14 days. The virus then moves to the semilunar ganglion and can be reactivated by stress, changes in the immune system, or trauma.

Treatment is symptomatic. It includes systemic analgesics (eg, acetaminophen) and topical anesthetics applied directly with a swab (eg, dyclonine 0.5% liquid or benzocaine 2 to 20% ointment). When many large areas are affected, 5% lidocaine viscous may be used as a mouth rinse 5 min before meal time. (NOTE: Lidocaine must not be swallowed because it anesthetizes the oropharynx, hypopharynx, and possibly epiglottis. Children must be watched for signs of aspiration.)

Secondary herpes simplex outbreaks occur as cold sores on the vermilion border of the lip or, much less commonly, as ulcerations of the mucosa of the hard palate. Usually, a patient notes a prodromal sensation, typically a tingling or burning of the lip. During the prodromal phase, treatment with oral acyclovir 200 mg five times a day can lessen the duration and severity of the outbreak. Topical acyclovir does not help. The duration of the lesions may be decreased by about a day by applying penciclovir 1% cream q 2 h while awake. It should be started during the prodrome or immediately upon the first appearance of a lesion.

Secondary herpes zoster (shingles) can occur intraorally (see HERPESVIRUS INFECTIONS in Ch. 162). It is uncommon but should be suspected when there is a sharp unilateral distribution of herpetiform lesions. No primary intraoral prodromal lesion occurs.

RECURRENT APHTHOUS STOMATITIS

(Recurrent Aphthous Ulcers; Canker Sores)

Typically, minor aphthae (< 1 cm in diameter, usually < 5 mm) occur singly or in small clusters and heal without scarring. They are white circular lesions surrounded by an erythematous margin. The central area consists of necrotic epithelial cells and debris, which when wiped off, reveal a red base. Major aphthae (periadenitis mucosa necrotica recurrens) are lesions > 1 cm. They persist for weeks and leave a scar after healing. They may recur every few years or may occur continually, with new lesions appearing before old ones heal.

Aphthae occur on movable, typically nonkeratinized tissue (eg, on the inner surface of the lips and on the buccal and alveolar mucosa, tongue, soft palate, oropharynx, and floor of the mouth), distinguishing them from herpetic lesions, which may appear similar initially but occur also on the immovable keratinized mucosal areas of the mouth (ie, the gingiva and hard palate). For their size, aphthous ulcers are disproportionately painful. The pain tends to subside after 4 to 6 days, and the lesions heal in 10 to 14 days.

Treatment

Usually, no treatment is needed. A topical anesthetic, such as 2% lidocaine viscous 5 mL (1 tsp), as an oral rinse q 3 h or before meals provides short-term relief and facilitates eating. A carboxymethylcellulose mucosal protective paste (Orabase, with or without 0.1% triamcinolone) applied qid prevents irritation of the ulcers by teeth, dental appliances, and oral fluids. It also reduces discomfort and promotes healing. Chemical or physical cautery can be used to decrease the pain. Silver nitrate sticks have been used, but low-power (2- to 3-watt), defocused, pulsed-mode application of energy from a CO_2 laser can provide relief almost instantaneously. Minor aphthae tend not to recur at a previously lased site.

For a large outbreak of aphthae, a suspension of tetracycline 125 mg/mL (made by dissolving the contents of a capsule in a teaspoon of water) may be swished in the mouth for 1 to 2 min, then expectorated. This treatment is repeated qid until symptoms are relieved, usually in one day. Alternatively, tetracycline oral suspension (250 mg qid for 10 days) is held in the mouth for 2 to 5 min, then swallowed. Early treatment, started when the patient senses a prodrome, may abort an outbreak. Tetracycline should not be given to children < 9 yr old because it discolors the developing teeth. Another option is rinsing with 1 tsp of 0.12% chlorhexidine for 30 sec bid. This rinse also often darkens teeth, but a dentist can remove the discoloration relatively easily in young patients who do not have significant root exposure.

For severe episodes of minor aphthae or for major aphthae, treatment consists of both topical and systemic corticosteroid therapy (eg, 1 tsp of dexamethasone elixir 0.5 mg/5 mL to rinse with, then expectorate, after meals and at bedtime for 5 days; prednisone 40 mg/day po initially, tapered over 10 days). Viscous lidocaine provides relief. Topical 0.05% fluocinonide gel tid may be applied to major aphthae. A palliative mouth rinse can be made with Dimetapp elixir 40 mL, Kaopectate 80 mL, and distilled water 120 mL. It must be shaken well before use. One tsp is swished for 1 to 2 min, then expectorated. It is used ad libitum.

ORAL ERYTHEMA MULTIFORME

Acutely painful stomatitis characterized by diffuse hemorrhagic lesions of the lips and oral mucosa, usually with constitutional symptoms.

Oral, ocular, and genital lesions can occur concurrently with dermal lesions and may be extensive, even without dermal lesions (see also ERYTHEMA MULTIFORME in Ch. 118).

Symptoms, Signs, and Diagnosis

Prodromal symptoms may include rhinitis and sinusitis. Multiple vesicles form in the earliest stage. Severe constitutional symptoms (fever, malaise, arthralgia) then develop and usually persist for 4 or 5 days. As they regress, the typical widespread hemorrhagic ulcerations develop. The lips are commonly bloody and crusted, but unlike in pemphigus and pemphigoid, the gingivae are rarely affected.

Erythema multiforme must be differentiated from allergic stomatitis, primary acute herpetic stomatitis, and, more rarely (in adults), pemphigus, all of which may produce similar constitutional symptoms. Allergic stomatitis can usually be suspected from the history.

Treatment

In the acute phase, oral lesions may be treated with systemic corticosteroids (prednisone 10 mg po tid for 5 days) or dexamethasone elixir 0.5 mg/5 mL (1 tsp qid for 5 days) as a rinse, which is then swallowed. A warm mouthwash of 10% sodium bicarbonate solu-

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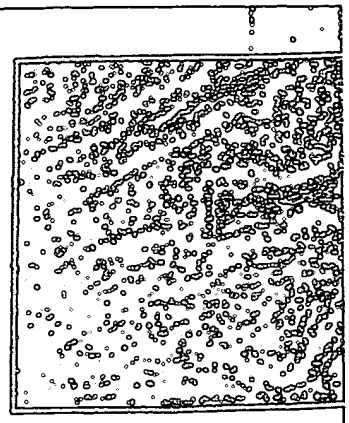

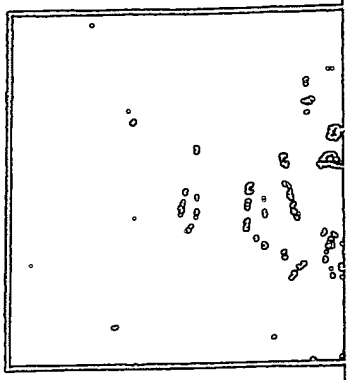

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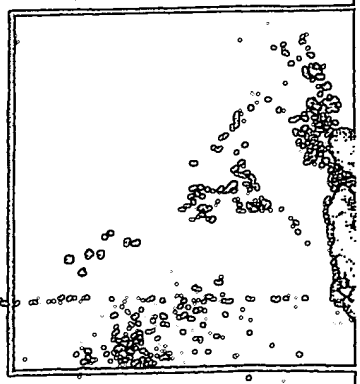

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Oral Pathology

Third Edition

J. V. SOAMES

Professor of Oral Pathology
University of Newcastle upon Tyne

AND

J. C. SOUTHAM

Emeritus Professor of Oral Medicine and Oral Pathology
University of Edinburgh

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12 Oral ulceration and vesiculobullous diseases

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UNIVERSITY PRESS
Great Clarendon Street, Oxford OX2 6DP
Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide in
Oxford New York
Auckland Bangkok Buenos Aires Cape Town Chennai
Dar es Salaam Delhi Hong Kong Istanbul Karachi Kolkata
Kuala Lumpur Madrid Melbourne Mexico City Mumbai Nairobi
São Paulo Shanghai Singapore Taipei Tokyo Toronto
with an associated company in Berlin
Oxford is a registered trade mark of Oxford University Press
in the UK and in certain other countries
Published in the United States
by Oxford University Press Inc., New York

First published 1985
Reprinted 1988, 1989, 1990 (with corrections), 1991
Second edition 1993
Reprinted 1995, 1996
Third edition 1998
Reprinted 1999, 2001, 2002

A catalogue record for this book is available from the British Library
Library of Congress Cataloging in Publication Data
Soames, J. V.
Oral Pathology / J. V. Soames and J. C. Southam.—3rd ed.
Includes bibliographical references and index.
1. Mouth—Diseases. 2. Teeth—Diseases. I. Southam, J. C.
II. Title.
[DNLM: 1. Stomatognathic System—pathology. WU 140 S676o 1998]
RC815.S59 1998
617.5'22—dc21
DNLM/DEC
for Library of Congress 97-34803 CIP
ISBN 0 19 262895 X (hbk)
ISBN 0 19 262894 1 (pbk)
Printed in China

12 Oral ulceration and vesiculobullous diseases

CLASSIFICATION OF ORAL ULCERATION

Injury to the oral mucosa, from whatever cause, may result in a localized defect of the surface in which the covering epithelium is destroyed leaving an inflamed area of exposed connective tissue. Such defects are called ulcers or erosions, the latter term sometimes being used to describe a superficial ulcer. Ulceration is the most common lesion of the oral mucosa and is a manifestation of many local and general disorders. Oral ulceration may be classified on an aetiological basis and the main causes are listed in Table 12.1. Several of these conditions are dealt with elsewhere in this book. This chapter is primarily concerned with traumatic ulceration, recurrent aphthous stomatitis, and ulceration associated with systemic diseases and the vesiculobullous diseases.

Table 12.1 Causes of oral ulceration

1. *Infective*
   - Bacterial
   - Viral
   - Fungal
2. *Traumatic*
   - Mechanical
   - Chemical
   - Thermal
   - Factitious injury
   - Radiation
   - Eosinophilic ulcer (traumatic granuloma)
3. *Idiopathic*
   - Recurrent aphthous stomatitis
     - minor aphthous ulcers
     - major aphthous ulcers
     - herpetiform ulcers
4. *Associated with systemic disease*
   - Haematological diseases
   - Gastrointestinal tract diseases
   - Behçet syndrome
   - HIV infection
   - Other diseases
5. *Associated with dermatological diseases*
   - Lichen planus
   - Chronic discoid lupus erythematosus
   - Vesiculobullous diseases
6. *Neoplastic*
   - Squamous cell carcinoma
   - Other malignant neoplasms

TRAUMATIC ULCERATION

Mechanical trauma from biting, sharp cusps, outstanding teeth, or ill-fitting intra-oral appliances is a common cause of oral ulceration (Fig. 12.1). Such ulcers do not usually present a problem in clinical diagnosis, but three criteria should be fulfilled.

1. A cause of trauma must be identified.
2. The cause must fit the site, size and shape of the ulcer.
3. On removal of the cause, the ulcer must show signs of healing within 10 days.

Problems in diagnosis may arise with chronic traumatic ulcers, for example related to overextended flanges of a denture. Such ulcers may have been present for several weeks and may be deep crater-like lesions with rolled edges which are indurated on palpation because of surrounding fibrosis. Differentiation from a neoplastic ulcer may, therefore, be difficult. Biopsy is indicated when a presumed traumatic ulcer does not shown signs of healing within 10 days. A traumatic ulcer shows the histological features of chronic non-specific inflammation.

A wide variety of chemicals may cause oral ulceration. These include irritant or caustic agents used in dental practice that may be accidentally applied to the oral mucosa, and preparations used by patients in self-treatment of oral complaints. The latter include various antiseptic mouthwashes, particularly if inadequately diluted, and aspirin misused by some patients as a local obtundant for the relief of toothache. The caustic action of aspirin is dose- and time-related and reactions vary in severity from oedema through to necrosis of the epithelium. The oedematous epithelium resembles leukoedema; the necrotic epithelium presents as soggy white plaques which slough off to leave areas of ulceration (see Fig. 9.8).

Fig. 12.1 Traumatic ulcer due to lip biting.

Fig. 12.2 Traumatic ulcer due to thermal burn.

Ulceration due to acute thermal trauma, for example from taking very hot food or drink, can occur on any part of the oral mucosa but is most commonly seen in the palate (Fig. 12.2).

Factitious ulcers are self-inflicted and may be a manifestation of stress, anxiety or more severe emotional disturbance. Their appearances and distribution vary considerably depending on how they are induced. Common causes are biting or chewing of lips, cheeks or tongue, and damage, for example to the gingivae, from sharp finger-nails (Figs 12.3, 12.4).

In patients undergoing radiotherapy for head and neck cancer the oral mucosa may suffer immediate damage due to the direct effects of radiation on the cells, or delayed effects due to epithelial atrophy and damage to the underlying vascular bed. The immediate effects include erythema, radiation mucositis, and ulceration. These changes usually appear within 2–3 weeks and heal within a similar period, after completion of the therapy. Oedema due to obstruction of the regional lymphatics may also occur. The later effects of vascular damage and epithelial atrophy render the mucosa susceptible to trauma and even minimal trauma can cause ulceration which may take months to heal. Ulcers occurring at the site of the original neoplasm may be difficult to differentiate from recurrent tumour, but radiation ulcers are generally painful whereas this is not a common symptom of early malignant disease.

An unusual type of ulceration, sometimes referred to as eosinophilic ulcer, traumatic granuloma or eosinophilic granuloma of soft tissues, appears to be associated particularly with trauma and crush injury to muscle, although the pathogenesis of the lesion is unclear. It occurs most commonly on the tongue and presents clinically as a chronic, well-demarcated ulcer which may mimic a squamous cell carcinoma (Fig. 12.5). Histological examination shows an ulcer covered by a thick layer of fibrinous exudate with a dense, chronic inflammatory cell infiltrate in its base involving underlying damaged muscle. The deeper parts of the lesion are characterized by an infiltrate rich in histiocytes and eosinophils, as reflected in the various names applied to this lesion. However, true granulomas are not present and the condition has no relationship to eosinophilic granuloma of bone.

RECURRENT APHTHOUS STOMATITIS (RAS)

Although a variety of oral ulcers may recur, for example those associated with mechanical trauma and dermatological diseases, there is a group of idiopathic ulcers whose natural history is characterized by frequent recurrences over a number of years. It is to this group that the collective term recurrent aphthous stomatitis (RAS) is applied.

Fig. 12.3, 12.4 Factitious ulcer caused by finger-nail. Notice also bite marks on thumb.

Fig. 12.5 Eosinophilic ulcer (traumatic granuloma).

Fig. 12.3

Fig. 12.4

Fig. 12.5

The prevalence varies with the population studied, but a reasonable estimate would be that between 11 per cent and 20 per cent of the population may be affected. Generally, the condition is more common in females than males and in the majority of patients the onset of RAS is in the first three decades of life. Three types of ulcers are recognized, based primarily on their clinical features:

(1) minor aphthous ulcers;
(2) major aphthous ulcers;
(3) herpetiform ulcers.

In addition, any of the three types may be associated with Behcet syndrome (see later).

Clinical features of RAS

Prodromal symptoms described as soreness, burning, or prickling sensations are recognized by many patients 1–2 days before the onset of ulceration. The mucosa may appear normal at this stage or there may be erythematous macules at the sites of future ulcers. The salient clinical features of the three types of RAS are listed in Table 12.2.

Minor aphthous ulceration

Minor aphthous ulceration accounts for 80 per cent or more cases of RAS. The condition is characterized by the occurrence of from one to five shallow round or oval ulcers which affect the non-keratinized areas of the oral mucosa (Figs 12.6, 12.7). The ulcers are less than 10 mm in diameter (generally they are about 4–5 mm across), and have a grey/yellow base with an erythematous margin. They heal without scarring, usually within 7–10 days, and they tend to recur at 1–4 month intervals, although this is very variable.

Major aphthous ulceration

Major aphthous ulcers are larger than minor aphthae and are usually greater than 10 mm in diameter (Fig. 12.8). They may occur at any of the sites of minor aphthae but may also involve the keratinized oral mucosa and commonly the soft palate, tonsillar areas, and oropharynx. The number of ulcers varies from one to ten and they may take 4–6 weeks to heal, and may heal with scarring. They tend to recur at less than monthly intervals, so that in severe cases ulceration of the oral cavity is virtually continuous and may be associated with severe

Table 12.2 Clinical features of recurrent aphthous stomatitis

	Minor	Major	Herpetiform
Age of onset (years)	10–19	10–19	20–29
Number of ulcers	1–5	1–10	10–100
Size of ulcers (mm)	< 10	> 10	1–2 but often coalesce
Duration (days)	7–14	> 30	10–30
Principal sites	Lips, cheeks, tongue	As for minor plus palate, pharynx	As for minor plus floor of mouth, palate, pharynx, and gingiva

Fig. 12.6 Minor aphthous ulceration.

Fig. 12.7 Minor aphthous ulceration.

Fig. 12.8 Major aphthous ulceration.

discomfort and with difficulty in eating and speaking. Unlike the shallow ulceration of minor aphthae, major aphthae extend deeper and may present as crater-like ulcers with rolled margins which are indurated on palpation because of underlying fibrosis. Differentiation of an isolated lesion from a malignant ulcer may be difficult. It should be appreciated that major and minor aphthae represent a spectrum of the same disease process and intermediate forms may be seen.

Key point

Recurrent aphthous stomatitis

- differential diagnosis of the three subtypes is based entirely on clinical features.

Herpetiform ulceration

Herpetiform ulceration is characterized by multiple, small, pinhead sized ulcers (about 1–2 mm across) that can occur on any part of the oral mucosa (Fig. 12.9). As many as a hundred ulcers may be present. When several ulcers are clustered together, confluence can result in larger areas of ulceration of irregular outline. The ulcers usually heal within 2–3 weeks. Large confluent ulcers may take longer and may heal with scarring, but this is not otherwise prominent. The ulcers tend to recur at less than monthly intervals and, as for major aphthae, may be associated with severe discomfort.

Aetiology of RAS

The aetiology of RAS is far from clear, but there is increasing evidence that damaging immune responses are involved. In addition, a number of local and general factors have also been incriminated (Table 12.3) and one or more of these may play a contributory role in a proportion of cases. These factors include the following.

Hereditary predisposition

A family history is found in up to 45 per cent of patients, but the mode and pattern of inheritance has not been established. Although some studies have suggested an increased prevalence associated with certain of the genetically determined histocompatibility antigens, no consistent patterns have been established.

Table 12.3 Aetiological factors in recurrent aphthous stomatitis

Hereditary predisposition
Trauma
Emotional stress and other psychological factors
Bacterial and viral infection
Allergic disorders
Haematological and deficiency disorders
Gastrointestinal diseases
Hormonal disturbance

Fig. 12.9 Herpetiform ulceration.

However, HLA-B51, which is strongly associated with Behçet syndrome, appears to have a negative association with RAS and this may help to differentiate the conditions. Although the genetic basis predisposing to RAS is far from understood, immune responses play a role in the pathogenesis of many of the diseases known to be associated with HLA antigens in man.

Trauma

Trauma may precipitate and influence the site of some ulcers but does not play an essential role in the aetiology of RAS.

Emotional stress

Epidemiological studies have suggested that emotional stress may be a precipitating factor but it is unlikely to be the direct cause of ulceration. Stress may also be associated with pernicious habits, such as cheek biting, which may precipitate and influence the pattern of ulceration. Cigarette smoking has been reported to protect against RAS, and the onset of RAS in some patients has been associated with cessation of tobacco smoking. Whether the protective effect is related to increased keratinization of the mucosa or to a systemic mechanism is unknown.

Infective agents

Various microorganisms have been isolated from recurrent oral ulcers but attempts to incriminate them as causal factors have been largely unsuccessful. Hypersensitivity to *Streptococcus sanguis* antigens has been implicated in the pathogenesis of RAS, but studies of hypersensitivity to the organism in patients and control subjects have produced conflicting results. Nevertheless, there is some evidence of cross-reacting antigens between *Streptococcus sanguis* and oral mucosa and there is a possibility that these could be involved in the immunopathogenesis of RAS.

A viral aetiology for herpetiform ulceration has been suggested but there is little evidence to support such a hypothesis. Although clinically the ulceration is similar to that produced by infection with herpes simplex virus (hence herpetiform), herpes simplex virus is not associated with the ulcers.

Adenoviruses have been isolated occasionally from RAS but there is no evidence that they are causal. They are ubiquitous organisms and their presence may be purely incidental, as so-called passenger viruses. A rise in IgM antibody titres to varicella-zoster virus and to cytomegalovirus has also been reported during recurrences, but the significance of this is unknown.

Allergic disorders

Some patients with RAS associate the onset of ulceration with certain foods and this, together with the raised level of IgE found in some patients, has led to the claim that food allergies play a role in the aetiology of RAS. However, the evidence is often anecdotal, and results from controlled studies in which patients were challenged with specific foods are inconclusive.

Haematological disorders

Haematological abnormalities associated with deficiencies of haematinics may be found in up to 20 per cent of patients with RAS. Iron (ferritin) deficiency, which may or may not be associated with anaemia, occurs most frequently, but in the

majority of patients no underlying cause can be identified. Deficiencies of folate and/or vitamin B_{12} are also associated with RAS, but much less frequently than iron.

The role of haematological deficiency states in the aetiology of RAS is unclear although it is known that deficiencies of iron, folate, vitamin B_{12} can produce atrophic changes in the oral mucosa. However, the ulceration in some patients improves when the deficiency is corrected, suggesting a causal role.

In some patients haematological deficiency states are secondary to gastrointestinal disease.

Gastrointestinal diseases

RAS has been reported in patients with a variety of gastrointestinal diseases some of which are associated with secondary haematological abnormalities as a result of malabsorption or chronic blood loss. An association with coeliac disease (idiopathic steatorrhoea or gluten sensitive enteropathy) is well recognized, but the incidence of coeliac disease in patients with RAS is low, probably only about 2–4 per cent. In contrast RAS, usually of the minor aphthous type, is a common symptom amongst patients with coeliac disease. RAS may also be seen in patients with ulcerative colitis and Crohn's disease.

Key points

Aetiology of RAS

- cause remains unknown
- haematinic deficiency and/or underlying systemic disease associated in a minority of patients
- a variety of factors may operate in an individual patient

Hormonal disturbance

In a small number of female patients a relationship between RAS and the menstrual cycle has been reported. It has been suggested that the degree of cornification of the mucosa is reduced in the low oestrogen, premenstrual phase and that this may render the mucosa more susceptible to trauma which could trigger the ulcers. Further evidence of a hormonal association in some patients is suggested by observations that the onset of ulceration may coincide with puberty and that remissions may occur in pregnancy. However, a recent extensive retrospective review of the literature concluded that no associations between RAS and the premenstrual period, pregnancy, or the menopause has been established.

Immunological and histopathological features of RAS

Although the aetiology of RAS is unknown there is considerable evidence that immune mechanisms are associated with the pathogenesis of the lesions.

Circulating antibodies to oral mucosal antigens have been demonstrated in 70–80 per cent of patients with minor or major aphthae and in patients with Behçet syndrome as compared with 10 per cent of controls, but their role in the pathogenesis of the lesions is uncertain. They maintain a relatively constant level and do not fluctuate with periods of activity and remission of ulceration, therefore, they may be simply a reflection of epithelial damage due to some other cause. However, patients with RAS have enhanced antibody-dependent cellular cytotoxicity activity (ADCC) early in the disease, suggesting a role for such a mechanism in the pathogenesis of the ulcers. Circulating immune complexes have also been demonstrated in some patients with RAS and in patients with

mimic pemphigoid while later it resembles the dermolytic type of epidermolysis bullosa.

Oral blood blisters (angina bullosa haemorrhagica)

Spontaneous blood-filled bullae (blisters) occasionally develop on the oral mucosa to which the term angina bullosa haemorrhagica has been applied. They may be up to 2–3 cm in diameter and occur on any part of the oral mucosa, although they are seen most commonly on the palate (Fig. 12.28). The patient may notice a pricking sensation when the blister arises and if large it may be uncomfortable. Early perforation is frequent, leaving an ulcer which heals unevenfully. Histology shows a subepithelial bulla with separation within the basement membrane zone (Fig. 12.29). Immunological findings are negative and no abnormalities in blood coagulation or in the tissues have been identified. The cause remains a mystery but it is probable that the bullae are related to trauma.

Fig. 12.28 Recently ruptured oral blood blister.

Fig. 12.29 Subepithelial bulla associated with oral blood blister.

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Behçet syndrome, the amount of immune complex being closely associated with disease activity. Immune complexes may cause tissue damage by activating complement. Despite these observations it appears unlikely that humoral immune mechanisms play a significant role in the pathogenesis of RAS.

In contrast, there is strong evidence that T-cell reactions are implicated in RAS from both histopathological and immunological studies. Microscopic examination of preulcerative lesions (premonitory stage) shows focal vacuolation and degeneration of suprabasal epithelial cells accompanied by a mononuclear, mainly lymphocytic, infiltrate in the lamina propria. In the deeper parts of the lesion the infiltrate has a mainly perivascular distribution and a similar pattern is seen in some other type IV delayed hypersensitivity reactions. Small numbers of lymphoid cells also infiltrate the epithelium. As the ulcerative stage approaches there is increased infiltration of the tissues, particularly the epithelium, by mononuclear cells accompanied by more extensive oedema and degeneration of the epithelium progressing to frank ulceration. Ultrastructural studies have demonstrated that the degeneration of prickle cells is associated with apoptosis and that the apoptotic debris is phagocytosed by macrophages in the mononuclear infiltrate. As the epithelium breaks down the cellular exudate becomes more mixed and includes large numbers of neutrophil leucocytes. These features resemble those seen in lichen planus except that in RAS the epithelial damage is not confined to the basal strata.

Immunohistochemical studies have shown changes in the T-cell subpopulations as the ulcers develop. The preulcerative lesion is characterized by mainly CD4 positive (inducer/helper) lymphocytes with smaller numbers of CD8 (suppressor/cytotoxic) cells in a ratio of about 2:1 (CD4:CD8). In contrast, the ulcerative stage is characterized by a marked increase in CD8 cells (CD4:CD8 approximately 1:10). As the ulcerative phase ends and the healing lesions becomes established there is a striking reversal of this ratio and CD4 cells predominate (CD4:CD8 approximately 10:1). These cyclical changes support a role for lymphocytotoxicity in the pathogenesis of the ulcers. It has been shown that peripheral blood lymphocytes from patients with RAS are cytotoxic to oral epithelial cells. The cytokine tumour necrosis factor (TNF) is also elevated in such lymphocytes suggesting that it may be involved in cell lysis.

Pathogenesis of RAS

- T cell reactions are involved
- mechanisms resemble those implicated in lichen planus
- immune response against keratinocyte-associated antigen
- keratinocyte death mediated by cytotoxic T cells

Key points

Changes in the expression of histocompatibility antigens by epithelial cells in RAS lesions accompany the changes in T-cell subpopulations, similar to those described for lichen planus in Chapter 9. In particular, the epithelial cells express the class II major histocompatibility antigens which are normally only expressed by immunocompetent cells. In the preulcerative stage these class II MHC antigens are found on the plasma membranes of the basal cells, but as the ulcerative phase develops they are expressed throughout the thickness of the epithelium. Expression declines to zero as the ulcers heal. Whether or not these changes play an active role in the pathogenesis of RAS has yet to be determined. They may merely reflect changes in lymphocyte populations and cytokine production.

In conclusion, the pathogenesis of RAS is similar to that of lichen planus. There is infiltration of the epithelium by T lymphocytes (epidermotropism) in response to some, as yet, unidentified keratinocyte-associated antigen. This

results in the differentiation of cytotoxic T cells and T cell mediated cell death throughout all strata of the epithelium, probably involving TNF. However, why epithelial cell death is so focal in RAS, producing the discrete and varying patterns of ulceration seen clinically, is unknown.

Behçet syndrome

Behçet syndrome is a rare disease originally characterized by the classical triad of RAS of any of the types listed above, genital ulceration, and eye lesions, especially uveitis. However, not all patients show the classical triad (although 90 per cent or more have RAS), and a variety of other manifestations, which include cutaneous, joint, neurological, vascular, and intestinal disorders, are now recognized as components of the syndrome. The disease is more common in males than in females and occurs especially in Japan.

On clinical and prognostic grounds Behçet syndrome can be divided into various subgroups, although these should not be regarded as distinct entities but as representing a spectrum of activity. The main clinical types are:

1. *Mucocutaneous type*: the mouth, genitals, skin, and conjuctiva may be involved.
2. *Arthritic type*: involvement of one or more large joints in addition to one or more of the manifestations of the mucocutaneous type.
3. *Neurological type*: involvement of the central nervous system in addition to some or all of the manifestations of types 1 and 2.
4. *Ocular type*: uveitis in addition to some or all of the manifestations of types 1, 2, and 3.

The aetiology of Behçet syndrome is unknown but there is a strong association with the histocompatibility antigen HLA-B51. Many of the systemic manifestations are probably related to the deposition of immune complexes.

VESICULOBULLOUS DISEASES

The vesiculobullous diseases are included in this chapter because they usually present as oral ulceration following rupture of the vesicles or bullae. The latter are collections of clear fluid within or just below the epithelium, which patients may refer to as blisters. The distinction between a vesicle and a bulla is simply one of size, the distinction being somewhat arbitary, but the term bulla is generally applied to a lesion greater than 5 mm in diameter.

Classification

The vesiculobullous diseases are divided into two major groups depending on the histological location of the lesions. In the first, the lesions form within the epithelium—intraepithelial vesicles; in the second, they form between the epithelium and the lamina propria (or dermis of the skin)—subepithelial vesicles.

The intraepithelial vesiculobullous diseases can be subdivided into two groups depending on the mechanisms of formation of the lesion:

1. Acantholytic vesicles and bullae, for example pemphigus. The lesions are produced by breakdown of the specialized intercellular attachments (desmosomes) between epithelial cells.
2. Non-acantholytic vesicles and bullae, for example viral infections of oral mucosa. The lesions are produced by death and rupture of groups of epithelial cells.

The main vesiculobullous diseases which may affect the oral mucosa are listed in Table 12.4.

Erythema multiforme is listed in the subepithelial group for convenience although, as its name implies, the manifestations are very variable and may include intraepithelial vesicles. Some forms of epidermolysis bullosa are also associated with intraepithelial vesicles but the majority are subepithelial in type.

The viral infections have been dealt with in Chapter 11. Darier's disease and bullous lichen planus are discussed in Chapter 9 since they usually present in the mouth as white lesions. The remaining conditions are all uncommon and are essentially skin diseases with oral manifestations.

Pemphigus

Pemphigus is an uncommon autoimmune disease which exists in several clinical forms, the most common and most severe being pemphigus vulgaris. This usually presents in middle-age, predominantly in women, and occurs more commonly in Ashkenazi Jews than in other ethnic groups. It is characterized by widespread bullous eruptions involving the skin (Fig. 12.10) and mucous membranes. The oral mucosa is ultimately involved in nearly all patients and in about 50 per cent of cases is the site of the initial lesions. In some patients the disease remains confined to the oral cavity. The bullae are fragile and readily rupture forming crusted or weeping areas of denudation on the skin and irregular, ragged mucosal ulcers (Fig. 12.11). Any part of the oral mucosa may be involved but

Table 12.4 Vesiculobullous diseases affecting the oral mucosa

I. *Intraepithelial vesiculobullous diseases*
- Acantholytic lesions
  - Pemphigus
    - pemphigus vulgaris
    - pemphigus foliaceous
    - pemphigus vegetans
  - Familial benign chronic pemphigus (Hailey–Hailey disease)
  - Darier's disease
- Non-acantholytic lesions
  - Viral infections
    - herpes simplex infections
    - herpes zoster
    - coxsackie infections

II. *Subepithelial vesiculobullous diseases*
- Erythema multiforme
- Pemphigoid group
  - bullous pemphigoid
  - benign mucous membrane (cicatricial) pemphigoid
- Dermatitis herpetiformis
- Linear IgA disease
- Epidermolysis bullosa group
  - inherited forms
  - epidermolysis bullosa acquisita (acquired type)
- Oral blood blisters (angina bullosa haemorrhagica)
- Bullous lichen planus

Fig. 12.10 Skin bullae in pemphigus vulgaris.

Fig. 12.11 Ragged oral ulcers in pemphigus vulgaris.

Fig. 12.12 Intraepithelial vesicle in pemphigus vulgaris.

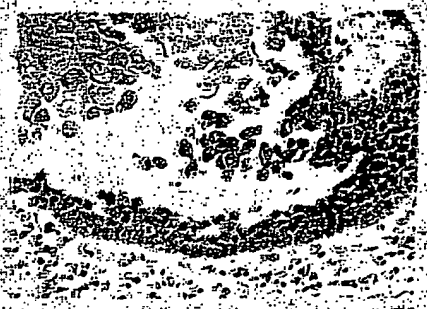


Fig. 12.13 Pemphigus vulgaris vesicle and acantholytic cells.

Fig. 12.14 Acantholytic (Tzanck) cells in smear from pemphigus vesicle.

Fig. 12.15 Immunofluorescent demonstration of epithelial-bound autoantibody in pemphigus bulla.

the soft palate, buccal mucosa, and gingiva are most frequently affected. T bullae are produced as a result of acantholysis and this process extends latera into the surrounding epithelium, often for a considerable distance. As a result this lateral extension the superficial layers of the epithelium can be slid over a detached from the deeper layers by gentle lateral pressure (Nikolsky's sign). T lateral extension also allows pressure exerted by the accumulation of fluid with the blister to dissipate so the bullae tend to be flaccid rather than tense.

Before the introduction of corticosteroid therapy the prognosis was very po and many patients survived less than two years following the onset of lesion Treatment with high doses of corticosteroids and other immunosuppressants h significantly reduced the mortality and in many patients the disease can now l controlled with prolonged remissions being reported.

Histological examination shows characteristic intraepithelial vesicles or bulli and cleft-like spaces produced by acantholysis. Typically, these changes occu between stratum spinosum cells just above the basal cell layer (Fig. 12.12). T basal cells forming the base of the lesion remain attached to the lamina propr and project into the bulla like a row of tombstones. There is remarkably litt inflammatory cell infiltration until the lesion ruptures, but occasional eosinophi may be seen in the epithelium in early lesions. Acantholytic stratum spinosum cells occurring singly or in small clumps are found lying free within the bliste fluid (Fig. 12.13). Unlike normal polyhedral stratum spinosum cells they ar small and rounded and contain enlarged hyperchromatic nuclei (Tzanck cells. Their identification in cytological smears taken from a blister is helpful in estab lishing a diagnosis (Fig. 12.14).

Immunological studies are important in establishing and confirming the diag nosis. Pemphigus is an autoimmune disease, and circulating autoantibodies t the intercellular substance of stratified squamous epithelium can be demon strated in the serum of patients. The antibodies are predominantly of the IgG class, but IgM and occasionally IgA classes may be represented. The autoanti body titre is correlated with the severity of the disease, and repeated tests or patients' sera to detect changes in titre may be helpful in assessing the clinica course of the disease and response to treatment. However, circulating pemphi gus-like antibodies occasionally appear in association with other conditions, for example following severe burns. Direct binding of autoantibodies to the intercel lular substance of stratum spinosum cells can also be demonstrated by immuno fluorescent techniques applied to biopsy specimens from involved epithelial (Fig. 12.15). The autoantibodies are thought to be responsible for the acantholysis as discussed below.

Oral lesions have also been reported in pemphigus foliaceous, where acantholysis occurs at a higher level in the epithelium, and in pemphigus vegetans. The latter is considered to be a milder form of pemphigus vulgaris and is character ized by the formation of vegetative masses of exuberant granulation tissue which develop following rupture of the bullae. Although any part of the oral mucosa may be involved, in most of the reported cases the lesions have involved the angles of the mouth.

There is considerable experimental evidence that the autoantibodies in pemphi gus are involved in acantholysis and that the acantholytic activity resides in the IgG fraction. Three main mechanisms have been proposed:

Complement activation via the classical pathway resulting in generation of lytic activity

Experimental studies suggest this is probably not an important mechanism. Acantholysis can be induced in explants of skin in organ culture by complement-free pemphigus serum.

Pemphigus

Key points

- intraepithelial, acantholytic vesicles and bullae
- ragged oral ulcers
- oral lesions often the presenting feature
- autoantibodies to desmosomal protein

Protease production

Binding of the autoantibody to antigen on the surface of epithelial cells results in the release of proteolytic activity which causes acantholysis. There is evidence that this is associated with activation of tissue plasminogen within the epithelium and generation of the proteolytic enzyme plasmin, which is then thought to be responsible for degradation of cell adhesion molecules. However, increased production of plasminogen activator by keratinocytes is seen in other diseases of skin not associated with acantholysis.

Direct binding of autoantibody to intercellular adhesion molecules

Recent studies have shown that the pemphigus antigen is a protein component of the desmosome belonging to the cadherin family. These transmembrane proteins are involved in cell–cell adhesion, and it is proposed that binding of the antibody to the proteins in the desmosomes prevents cell–cell adhesion directly by steric interference. Once acantholysis is initiated, plasminogen release and complement-mediated lysis may amplify the process.

Familial benign chronic pemphigus (Hailey-Hailey disease)

This rare and relatively benign disorder has an autosomal dominant pattern of inheritance and is characterized by recurrent acantholytic vesicular eruptions on the skin. Oral involvement has been reported. Despite the acantholysis the immunological findings are negative and this, together with the family history, helps differentiate it from pemphigus vulgaris.

Erythema multiforme

Erythema multiforme is a disease of abrupt onset involving skin and mucous membranes and has a wide range of clinical presentations, hence 'multiforme'. The pathogenesis of the disease is unknown, although many precipitating factors have been implicated including drugs (particularly sulphonamides) and preceding infection (especially herpes simplex infection). However, many cases appear to arise spontaneously. It has been suggested that the disease represents a hypersensitivity reaction and that the manifestations may be related to deposition of immune complexes in which the antigen may be of drug, bacterial, or viral origin.

Erythema multiforme occurs mainly in young adults and is more common in males than in females. There may be a prodromal phase with upper respiratory infection, headache, malaise, nausea, and sometimes arthralgia. The severity of the disease varies considerably. In its most severe form, the Stevens–Johnson syndrome, there is widespread involvement of the skin and oral, genital, and ocular mucosae. Ocular involvement (Fig. 12.16) can lead to conjunctival scarring and visual impairment. Milder forms usually involve the oral mucosa, with or without skin lesions, or the skin alone may be involved. Generally, the disease tends to subside after 10–14 days but recurrences may occur. Recurrent erythema multiforme is associated in particular with recurrent attacks of herpes simplex virus infection.

Fig. 12.16 Ocular lesions in erythema multiforme.

Fig. 12.17 Target skin lesions in erythema multiforme.

The skin lesions have a variety of forms, including erythematous macular rashes and vesiculobullous eruptions in addition to the characteristic and usually diagnostic target or iris lesions (Fig. 12.17). These consist of concentric rings of varying erythema and oedema in the centre of which may be an intact or ruptured and crusted bulla. The hands and feet are most commonly involved.

Oral lesions may involve any part of the mucosa, although the lips and anterior parts of the mouth are most commonly affected (Figs 12.18, 12.19). The appearance of the lesions varies with time. Erythematous patches are quickly followed by vesiculobullous eruptions which rapidly break down into erosions as the bullae disintegrate. The erosions on the lips are accompanied by bleeding and crusting. Circumoral crusting, haemorrhagic lesions are an important feature in arriving at a clinical diagnosis; somewhat similar lesions may be seen in association with herpetic gingivostomatitis.

Key points

Erythema multiforme

- mucosal vesicles and bullae variable
- oral ulceration/circumoral crusting, haemorrhagic lesions
- target/iris skin lesions
- precipitated by drugs/herpesvirus antigens
- immune complex vasculitis

The diagnosis of erythema multiforme is based primarily on the clinical findings. The histopathological features are non-specific (although biopsy may be useful to exclude other diseases) and a wide spectrum of histological changes has been described. Epithelial changes include inter- and intracellular oedema, with varying degrees of necrosis of keratinocytes leading to intraepithelial vesiculation. Alternatively, bullae may form subepithelially following degeneration of basal cells and detachment of the full thickness of the epithelium from the lamina propria (Fig. 12.20). The epithelium forming the lid of the bulla is often necrotic. The lamina propria is oedematous and there is a variable, mononuclear inflammatory cell infiltration which extends perivascularly into the deeper tissues.

Immunological findings in erythema multiforme are either negative or non-specific but deposits of IgM and C3 may be found in the superficial vessels, suggesting that the disease is mediated in part by deposition of immune complexes and a type III hypersensitivity reaction. Deposition of immune complexes leads to complement activation, chemotaxis of neutrophils, and vasculitis, resulting eventually in ischaemic necrosis of epithelium. Neutrophils may also release lysosomal enzymes which could cause direct damage to keratinocytes. Circulating immune complexes have been detected in patients with erythema multiforme and in some cases they have been associated with herpes simplex viral antigens.

Figs 12.18, 12.19 Oral lesions in erythema multiforme.

Fig. 12.20 Vesicle in erythema multiforme.

Fig. 12.18

Fig. 12.19

Fig. 12.20

Pemphigoid

The general heading of pemphigoid includes bullous pemphigoid and benign mucous membrane pemphigoid. The term benign is often omitted and the latter may also be referred to as cicatricial pemphigoid. It is probable that the conditions are related and represent manifestations of a spectrum of disease, although it may be possible to separate them on clinical and, to some extent, immunological grounds. Both are autoimmune disorders characterized by the formation of subepithelial bullae. Pemphigoid is about twice as common in women as men and the mean age of onset is about 60 years. The disease is not life-threatening but may run a chronic course over many years.

Bullous pemphigoid primarily involves the skin, presenting as large tense bullae typically involving the limbs and lower abdomen. Oral lesions occur in a minority of patients but it is very rare for these to precede the skin eruptions. When present, the oral manifestations are indistinguishable from those of benign mucous membrane pemphigoid.

In contrast, the oral mucosa is almost always affected in benign mucous membrane pemphigoid (Fig. 12.21), whereas the skin is only minimally involved. In most cases oral lesions precede those in other locations and may be the only manifestations of the disease.

Bullae, which are occasionally haemorrhagic, occur anywhere on the oral mucosa. Unlike those seen in pemphigus vulgaris they tend to be tense and because the lid consists of a full thickness epithelium, are relatively tough and may remain intact for a few days. When they rupture they give rise to erosions which heal slowly, sometimes with scarring, hence the alternative name for this disease—cicatricial pemphigoid (Fig. 12.22). Although bullae can occur on any part of the mucosa, the most consistent oral lesions in dentate patients, occurring in over 90 per cent of cases, involve the gingiva where the condition presents as desquamative gingivitis (Fig. 12.23). In some patients this is the only manifestation of the disease.

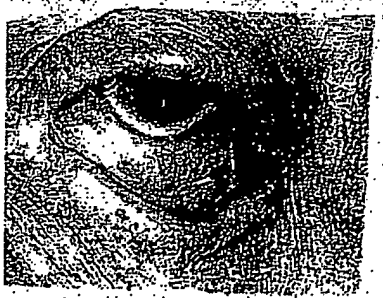
In addition to the oral mucosa the conjunctiva and mucosae of the nose, larynx, pharynx, oesophagus, and genitalia may be involved. Ocular involvement is the most serious complication with scarring leading to adhesions between the bulbar and palpebral conjunctiva, opacity of the cornea, and blindness (Fig. 12.24).

Histopathological examination of established pemphigoid lesions shows separation of the full thickness of the epithelium from the lamina propria producing a subepithelial bulla with a thick roof (Fig. 12.25). Developing bullae are characterized by foci of oedema in the basement membrane zone which enlarge to form vesicles. Initially, there is no evidence of an inflammatory reaction in the lamina propria but as the vesicle develops there is infiltration by variable numbers of neutrophils and eosinophils around and within the developing bulla. These changes

Fig. 12.21 Oral manifestations of benign mucous membrane pemphigoid showing intact vesicles.

Fig. 12.22 Extensive oral ulceration associated with benign mucous membrane pemphigoid.

Fig. 12.23 Benign mucous membrane pemphigoid presenting as desquamative gingivitis.



12.24

Fig. 12.25

Fig. 12.24 Ocular lesions in benign mucous membrane pemphigoid.

Fig. 12.25 Subepithelial bulla in benign mucous membrane pemphigoid.

Fig. 12.26 Linear binding of IgG in the basement membrane zone in benign mucous membrane pemphigoid.

are accompanied by a perivascular mononuclear, mainly lymphocytic, infiltrate in the lamina propria, the intensity of which increases as the lesion develops.

Electron microscopic studies have shown that separation occurs through the lamina lucida of the basement membrane, between the cell membranes of the basal cells and the lamina densa. Loss of hemidesmosomes and disorganization of tonofilaments within basal cells have also been described.

Immunopathological investigations involving direct immunofluorescence studies of fresh, unfixed biopsy material to detect tissue-bound immune product and indirect immunofluorescence techniques to detect circulating autoantibodies in the patient's serum are essential to establish the diagnosis (Table 12.5). In both bullous and benign mucous membrane pemphigoid, direct immunofluorescence shows linear binding of immunoglobulin, predominantly IgG but occasionally other classes, in the basement membrane zone (Fig. 12.26). Linear deposits of complement products, principally C3, are also bound to the basement membrane zone.

By indirect immunofluorescence techniques circulating autoantibodies of IgG type against basement membrane antigens of skin and mucosa can be demonstrated in about 75 per cent of patients with bullous pemphigoid. In contrast, the serum of patients with benign mucous membrane pemphigoid rarely contains circulating anti-basement membrane antibodies.

The immunopathological findings suggest that bulla formation involves binding of autoantibody, activation of complement, generation of chemotactic factors, and leucocyte-mediated damage associated with the accumulation and release of proteolytic enzymes from neutrophils. It is highly likely that the leucocyte-mediated damage also involves the activity of eosinophils.

Patients with bullous pemphigoid have antibodies to two hemidesmosome-associated antigens. One is located intracellularly, whilst the other is a transmembrane protein with intra- and extracellular components. The autoantigen in mucous membrane pemphigoid has not been precisely characterized but is thought to be similar or identical to the transmembrane protein identified in bullous pemphigoid.

Key points

Mucous membrane pemphigoid

- subepithelial vesicles and bullae
- occasionally intact oral vesicles and bullae
- extensive oral ulceration
- desquamative gingivitis
- autoantibodies to hemidesmosomal proteins

Dermatitis herpetiformis

Dermatitis herpetiformis is a chronic, intensely pruritic subepidermal autoimmune blistering disease of skin. Oral manifestations are variable and range from small symptomless erythematous areas to extensive erosions. Their incidence is difficult to establish but in some series they have been reported in up to 75 per cent of patients.

Histologically, the lesions are characterized by the formation of microabscesses at the tips of the connective tissue (dermal) papillae beneath the epithelium. Neutrophils predominate, but as the lesions develop increasing numbers of eosinophils are seen. Immunofluorescence studies show granular deposits of IgA in the tips of the connective tissue papillae together with complement components (Table 12.5). Activation of the alternative complement pathway by IgA

Table 12.5 Major immunological findings in subepithelial bullous disorders

Disease	Direct IF	Indirect IF (circulating antibodies)
Bullous pemphigoid	Linear IgG, C3: BM zone	Positive (75 %) IgG
Benign mucous membrane pemphigoid	Linear IgG, C3: BM zone	Negative
Dermatitis herpetiformis	Granular IgA, C3: tips of dermal papillae	Negative
Linear IgA disease	Linear IgA, C3: BM zone	Negative
Epidermolysis bullosa acquisita	Linear IgG, C3: BM zone	Positive (30–40 %) IgG

and the subsequent generation of chemotactic factors are thought to be important in the pathogenesis of the lesions, but T-lymphocyte reactions and cytokine release may also be involved.

Many patients with dermatitis herpetiformis also have abnormalities of their jejunal mucosa associated with gluten hypersensitivity, but the precise relationship between the intestinal, oral, and skin lesions is uncertain.

Linear IgA disease

This is a rare subepidermal blistering disease of skin which clinically overlaps with dermatitis herpetiformis and bullous pemphigoid. Oral lesions have been reported. Patients may have gluten hypersensitivity, but this is much less common than in dermatitis herpetiformis. There is a strong association with internal malignancy, especially lymphoma.

Immunopathological studies show linear binding of IgA along the basement membrane zone similar to the pattern seen in pemphigoid, but different from the clumped granular deposits of dermatitis herpetiformis (Table 12.5).

Epidermolysis bullosa

The inherited forms of epidermolysis bullosa form a diverse and complex group of syndromes of which over 30 types have been reported.

In general, they are characterized by the formation of skin bullae which may be manifest at birth or appear shortly afterwards. There is extreme fragility of the skin and the bullae usually develop in response to minimal trauma or pressure, but they may arise spontaneously. Hands, feet, knees, elbows, buttocks, and occiput are common sites. Oral and other mucosae may be involved. The bullae tend to heal slowly with scarring which can result in claw-like deformity of the hands (Fig. 12.27) and other complications, such as difficulties in eating, speaking, and swallowing as a result of involvement of the mouth, larynx, and pharynx. Several types are incompatible with life.

Currently the various types are classified into three major groups based on the histological level of bulla formation and the molecular basis of the defect:

1. *Epidermolytic (simplex types).* Separation occurs within the epithelium to produce intraepithelial bullae. This group results from mutation of the genes coding for keratins 5 and 14, expressed in basal keratinocytes.

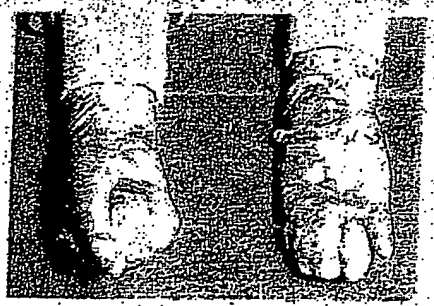


Fig. 12.27 Epidermolysis bullosa—scarring of hands.

2. *Junctional (gravis type).* Separation occurs within the lamina lucida to produce subepithelial bullae. This group is caused by mutations in the gene coding for a laminin associated with the anchoring filament–hemidesmosome complex of the basement membrane.
3. *Dermolytic (dystrophic type).* Separation occurs beneath the basal lamina to produce subepithelial bullae. Anchoring fibrils may be decreased in number and poorly developed. This group is due to mutation in the type VII collagen gene, the anchoring fibril collagen.

Classified in this way the different syndromes in each group tend to show similar clinical features and modes of inheritance (Table 12.6).

Oral lesions are seen mainly in the junctional and dermolytic types. Bullae may appear in neonates in response to suckling, and, later, minimal trauma from toothbrushing and routine dental treatment can cause serious consequences. The bullae rupture to leave painful erosions and subsequent scarring can restrict the opening of the mouth, movement of lips and tongue, and cause obliteration of the sulci. Effective oral hygiene may be impossible and rampant caries and its sequelae add to the dental complications. Dental defects, especially enamel hypoplasia, have been described in some patients.

Epidermolysis bullosa acquisita

This is an uncommon acquired blistering dermatosis characterized by subepithelial bullae. Oral bullae, ulceration, and scarring have been recorded in about half of the reported cases.

Separation occurs in or beneath the lamina densa and is associated with linear deposits of IgG and C3 in the basement membrane zone (see Table 12.5). Clinically, the disease has a wide range of presentations, but early stages may

Table 12.6 Principal modes of inheritance and main clinical features of the subgroups of epidermolysis bullosa

Type	Skin/general	Oral/mucosal	Inheritance
Epidermolytic (simplex)	Blisters present at birth Mild, no scarring Improvement at puberty	Absent or very mild Often abates Teeth normal	Autosomal dominant
Junctional (gravis)	Congenital blisters/erosions Extensive, generalized blistering, atrophy, prominent acral involvement Death common in infancy	Extensive involvement of all mucosae Severe dental abnormalities	Autosomal recessive
Dermolytic (dystrophic)	Congenital blisters/erosions Marked scarring, mitten deformity of hands, syndactyly, nail dystrophy	Oral and other mucosae often involved Hypoplastic teeth	Autosomal dominant